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| (21) International Application Number: PCT/EP96/01962 (22) International Filing Date: 9 May 1996 (09.05.96) (30) Priority Data: 195 17 430.5 12 May 1995 (12.05.95) DE (71) Applicant (for all designated States except US): BOEHRINGER MANNHEIM GMBH [DE/DE]; D-68298 Mannheim (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): OCHLICH, Peter-Paul [DE/DE]; Wallonenstrasse 34, D-69250 Schönau (DE). MÜLLER-BECKMANN, Bernd [DE/DE]; Auf dem Leimen 19, D-67269 Grünstadt (DE). (74) Agents: MINK, Reinhold et al.; Boehringer Mannheim GmbH, Patentabteilung, D-68298 Mannheim (DE). | | (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: PHARMACEUTICAL ADMINISTRATION FORM OF PARATHYROID HORMONE HAVING AN ACTIVE INGREDIENT RELEASE PERIOD OF FROM TWO TO SIX HOURS | | |
| (57) Abstract The present invention is directed to a pharmaceutical administration form of parathyroid hormone or parathyroid hormone derivatives having an active ingredient release period of from two to six hours, the use of parathyroid hormone for the preparation of such pharmaceutical administration forms, and to a method for treating osteoporosis in the human body. | | |

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5 **Pharmaceutical Administration Form of Parathyroid Hormone**
 Having an Active Ingredient Release Period of from Two to Six Hours

 The present invention is directed to a pharmaceutical administration form of parathyroid hormone or parathyroid hormone derivatives having an active ingredient release period
10 of from two to six hours, the use of parathyroid hormone in the treatment of osteoporosis by applying said pharmaceutical administration form, and a method for the treatment of osteoporosis in the human body.

 Parathyroid hormone and N-terminal parathyroid hormone fragments are known to have
15 osteogenous activity which has been observed in animal experimental studies on rats as well as in clinical studies on osteoporotic patients and has been described in technical literature (Selye, Endocrinology 16 (1932), 547-558; Hefti et al., Clin. Sci. 62 (1982), 389-396; Gunnes-Hey et al., Metab. Bone Dis. Relat. Res. 5 (1984), 177-181; Reeve et al., Br. Med. J. 280 (1980), 1340-1344; Slovik et al., J. Bone Miner. Res. 1 (1986), 377-
20 381, EP 0,197,514).

 There is general agreement in the art about the fact that the osteogenous activity of PTH is bound to a pulsatile or intermittent application. Pulsatile application of PTH in animal experimental as well as in clinical studies on patients resulted in an increase of bone
25 matter (Tam et al., Endocrinology 110(2) (1982), 506-512; Podbesek et al., Endocrinology 112(3) (1983), 1000-1006; Hock et al., J. Bone Miner. Res. 7(1) (1992), 65-72; Reeve et al., Br. Med. J. 280 (1980), 1340-1344; Slovik et al., J. Bone Miner. Res. 1 (1986), 377-381).

30 While in animal experiments an increased bone transformation rate was observed with continuous infusion of PTH, this, however, did not result in a net gain of bone matter (Tam et al., Endocrinology 110 (2) (1982), 506-512; Malluche et al., Am. J. Physiol.

242(2) (1982), F197-F201; Hock et al., J. Bone Miner. Res. 7(1) (1992), 65-72; Podbesek et al., Endocrinology 112(3) (1983), 1000-1006).

Surprisingly, it has now been found that continuous application of PTH or derivatives thereof certainly results in a net gain of bone matter, when limited to up to six hours.

Therefore, the invention is directed to a pharmaceutical administration form of PTH or derivatives thereof having an active ingredient release period of from two to six hours, and preferably of four hours. Here, the pharmaceutical administration form may be an infusion solution or a transdermic or enteric pharmaceutical system having an active ingredient release period of up to six hours. Compared to pulsatile application which in all hitherto known animal experimental and clinical studies has been effected as a daily subcutaneous injection, the transdermic or enteric application of PTH offers the decisive advantage of retarded active ingredient release. Abrupt PTH pulses and the associated substantial disturbance of the patient's well-being due to the necessary injection can be dismissed.

According to the present invention, the pharmaceutical administration form contains biologically active parathyroid hormone or parathyroid hormone derivatives, particularly human PTH(1-84) or an N-terminal human PTH fragment having the sequences 1-29 to 1-41, preferably the sequences 1-34, 1-35, 1-36, 1-37, or 1-38. Furthermore, PTH-analogous peptides, variants or modifications of parathyroid hormone (PTH agonists) resulting from the replacement of single or multiple amino acids in the amino acid sequence of unmodified parathyroid hormone may also be employed. In addition, PTH fragments appropriately abridged at the N terminus and/or the C terminus are also possible within the meaning of the invention. Such fragments have been described in WO 90/10067, EP 0,301,484 or EP 0,301,485, for example.

Application of the PTH peptides is effected in such a manner that release of the pharmacologically active substance in the body within a period of from 2 to 6 hours is ensured. Such release may be obtained in different ways. One method is to administer the

required amount of PTH intravenously over the appropriate period of time. Another method involves transdermic application, releasing the active ingredient within the desired period of time. This may be effected using a patch which is applied to the skin for the desired period of time. By adding permeation accelerators, release of the active ingredient through the skin as regularly as possible can be ensured so that during application of the patch to the skin, continuous release of the active ingredient and permeation through the skin take place. Another way of transdermic application involves iontophoresis. To this end, an appropriate dosage unit (iontophoretic patch) is applied to the skin, and release of the active ingredient through the skin within the desired period of time is controlled by applying an electrical potential.

Preferably, loaded liposomes, microspheres made of common polymers, or proteinoid complexes ensuring resorption of the active ingredient in the small intestine over an appropriate period of time are possible as enteric pharmaceutical systems.

According to the invention, PTH or a PTH fragment may be administered in the form of a continuous infusion preferably over two to six hours, particularly about four hours. Here, a tendency to higher anabolic activity can be observed following an infusion of about four hours compared to a one hour infusion or subcutaneous bolus administration. An exceedingly good osteogenous activity was observed following a four hour intravenous infusion of hPTH(1-34) on five working days within two successive weeks.

Further examinations using PTH(1-37) showed that levels maintained for 8 hours at 80 $\mu\text{g/kg}$ iv, i.e., at the same infusion rate as 40 $\mu\text{g/kg}$ iv over 4 hours, give rise to severe adverse effects on the bones, while at 40 $\mu\text{g/kg}$ PTH(1-37) iv over 4 hours a distinct osteoanabolic effect occurs. In contrast, intravenous bolus injection of 80 $\mu\text{g/kg}$ PTH(1-37) within about one minute does not result in negative but positive effects with respect to the relative X-ray density and the Ca content. However, the therapeutic utility of comparably high intravenous PTH doses in the form of a bolus administration is not deemed advantageous due to severe circulatory effects to be expected.

Preferably, water is used as injection medium, containing additives common with injection solutions, such as stabilizers, solubilizers and buffers. Such additives are, e.g., tartrate and citrate buffers, ethanol, complexing agents such as ethylenediaminetetraacetic acid and non-toxic salts thereof, high molecular weight polymers such as liquid
5 poly(ethylene oxide) for viscosity control. Liquid carrier substances must be sterile and are preferably filled into ampoules.

The dosage may depend on various factors such as mode of application, species, age or individual condition. Usually, from 30 to 50 $\mu\text{g/kg/day}$ are administered.

10

In addition, the invention relates to the use of parathyroid hormone or a parathyroid hormone derivative in the treatment of osteoporosis by application in the form of a continuous infusion for two to six hours or a transdermic or enteric administration form having an active ingredient release period of from two to six hours. Such examinations
15 relating to the use of PTH or PTH fragments, according to the invention, will be subject to protection, particularly within the scope of clinical tests for the purpose of authorization according to the drug law. As a rule, the corresponding petitioned authorization according to the drug law relates to the treatment of calcium-metabolic diseases in general and to the treatment of osteoporosis, in particular.

20

Likewise, the invention is directed to a method for osteoporosis treatment of the human body wherein, in order to increase the bone matter, a therapeutically effective amount of parathyroid hormone or parathyroid hormone derivative is applied in the form of a continuous infusion for two to six hours or a transdermic or enteric administration form
25 having an active ingredient release period of from two to six hours. Preferably, the method according to the invention is conducted within the scope of clinical tests for the purpose of authorization according to the drug law.

In the following, the invention will be illustrated in more detail by way of embodiments.

30

Example 1**Infusion of PTH for various periods of time**

5 In a pre-operation, a venous permanent catheter was implanted in male Wistar rats weighing about 230-250 g. The animals were assigned to 5 different groups of treatment of 6 animals each, which were treated as follows:

- 10 1. Rinsing the catheter with solvent on 5 working days within two successive weeks = negative control.
2. Intravenous infusion of hPTH(1-34), 40 µg/kg/day within one hour on 5 working days within two successive weeks.
- 15 3. Intravenous infusion of hPTH(1-34), 40 µg/kg/day within four hours on 5 working days within two successive weeks.
4. Intravenous infusion of hPTH(1-34), 40 µg/kg/day within eight hours on 5 working days within two successive weeks.
- 20 5. Subcutaneous bolus injection of hPTH(1-34), 40 µg/kg/day on 5 working days within two successive weeks = positive control.
- 25 6. In another experiment, PTH(1-37) was tested under various conditions. The comparison comprises intravenous infusion of 40 µg/kg and 80 µg/kg over four and eight hours, respectively, as well as subcutaneous injection of 40 µg/kg and intravenous bolus injection of 80 µg/kg.

30 On the third day following the last treatment, the animals were sacrificed and the femora were removed for subsequent analysis of femur weight, volume, dry weight, ash weight, and calcium content.

The results for PTH(1-34) are summarized in the following Table 1. showing that a significant increase of bone matter was observed in the Treatment Groups 1 (1 hour infusion), 2 (4 hours infusion) and 4 (sc bolus), while no differences compared to the control group occurred in Group 3 (8 hours infusion).

5

Table 1

Continuous infusion of PTH(1-34) on rats (Wistar)

Duration of treatment:

- 10 Continuous infusion for 1 hour (Group 1), 4 hours (Group 2), 8 hours (Group 3) once per day iv, and once per day subcutaneous (sc) (Group 4).

Dose: 40 µg PTH(1-34)/kg/day

n = 5 - 6

| Duration of infusion | Control | Group 1 1 hour iv | Group 2 4 hours iv | Group 3 8 hours iv | Group 4 sc |
|-------------------------------|----------------|------------------------------|-------------------------------|-------------------------------|-----------------------|
| <u>Length (mm)</u> | | | | | |
| Median | 34 | 34 | 34 | 34 | 34 |
| 1st quart. | 34 | 34 | 34 | 33 | 34 |
| 3rd quart. | 34 | 35 | 34 | 34 | 34 |
| <u>Volume (µl)</u> | | | | | |
| Median | 645 | 648 | 672 | 680 | 639 |
| 1st quart. | 628 | 639 | 645 | 642 | 627 |
| 3rd quart. | 675 | 670 | 679 | 683 | 668 |
| <u>Dry weight (mg)</u> | | | | | |
| Median | 458 | 499 | 520 | 471 | 512 |
| 1st quart. | 445 | 479 | 518 | 458 | 493 |
| 3rd quart. | 473 | 517 | 539 | 503 | 522 |
| <u>Ash weight (mg)</u> | | | | | |
| Median | 278 | 308 | 328 | 280 | 316 |
| 1st quart. | 270 | 296 | 323 | 278 | 306 |
| 3rd quart. | 288 | 320 | 337 | 308 | 321 |

| Duration of infusion | Control | Group 1 1 hour iv | Group 2 4 hours iv | Group 3 8 hours iv | Group 4 sc |
|---|----------------|------------------------------|-------------------------------|-------------------------------|-----------------------|
| <u>Ca content (mg)</u> | | | | | |
| Median | 100 | 113 | 123 | 102 | 115 |
| 1st quart. | 98 | 109 | 115 | 99 | 115 |
| 3rd quart. | 106 | 116 | 131 | 112 | 116 |
| <u>Dry Weight/Volume (mg/ml)</u> | | | | | |
| Median | 707 | 758 | 794 | 710 | 786 |
| 1st quart. | 682 | 747 | 773 | 671 | 776 |
| 3rd quart. | 715 | 784 | 820 | 740 | 795 |
| <u>Ash Weight/Volume (mg/ml)</u> | | | | | |
| Median | 428 | 468 | 497 | 433 | 488 |
| 1st quart. | 412 | 459 | 481 | 401 | 479 |
| 3rd quart. | 438 | 485 | 519 | 453 | 490 |
| <u>Ca Content/Volume (mg/ml)</u> | | | | | |
| Median | 155 | 171 | 192 | 155 | 175 |
| 1st quart. | 152 | 170 | 171 | 145 | 171 |
| 3rd quart. | 158 | 176 | 193 | 164 | 180 |

In one test series of PTH(1-37) the influence of duration at an identical infusion rate (40 µg/kg iv over four hours; 80 µg/kg iv over eight hours) was examined. Here, it appeared that a significant osteoanabolic effect occurred at 40 µg/kg PTH(1-37) iv over four hours, while the double infusion time period of eight hours at an overall amount of 80 µg/kg iv resulted in dramatic negative effects on the bone balance. In contrast, repeated intravenous bolus injection of 80 µg/kg within about one minute had a positive effect on the bone balance. However, the therapeutic utility of comparably high intravenous PTH doses in the form of a bolus administration is not deemed advantageous due to the relatively small effect and, in particular, due to severe circulatory effects to be expected.

The results for PTH(1-37) are summarized in Table 2.

5 **Table 2**

a) Effect of PTH(1-37) by intravenous infusion on rats

Duration of treatment: 10 working days, once per day

Dose: 40 (4 hours) and 80 (8 hours) $\mu\text{g/kg/day}$, respectively

10 Infusion rate: 10 $\mu\text{g/kg/hour}$

Group 1: 4 hours iv; 40 $\mu\text{g/kg/day}$

Group 2: 8 hours iv; 80 $\mu\text{g/kg/day}$

Group 3: subcutaneous (sc); 40 $\mu\text{g/kg/day}$

n = 7 - 10

15

| Duration of infusion | Control | Group 1 4 hours iv | Group 2 8 hours iv | Group 3 sc |
|--|---------|-----------------------|-----------------------|---------------|
| <u>Relative X-Ray Density (mmAl)</u> | | | | |
| Median | 1.5 | 2.0 | 1.5 | 1.8 |
| 1st quart. | 1.3 | 2.0 | 1.3 | 1.7 |
| 3rd quart. | 1.6 | 2.2 | 1.7 | 1.8 |
| <u>Length (mm)</u> | | | | |
| Median | 36 | 35 | 34 | 36 |
| 1st quart. | 35 | 35 | 34 | 36 |
| 3rd quart. | 36 | 36 | 35 | 36 |
| <u>Volume (μl)</u> | | | | |
| Median | 709 | 786 | 737 | 775 |
| 1st quart. | 659 | 752 | 692 | 710 |
| 3rd quart. | 735 | 803 | 831 | 814 |

| Duration of infusion | Control | Group 1 4 hours iv | Group 2 8 hours iv | Group 3 sc |
|---|----------------|-------------------------------|-------------------------------|-----------------------|
| <u>Dry Weight (mg)</u> | | | | |
| Median | 515 | 600 | 424 | 599 |
| 1st quart. | 476 | 581 | 420 | 570 |
| 3rd quart. | 535 | 608 | 500 | 633 |
| <u>Ash Weight (mg)</u> | | | | |
| Median | 329 | 381 | 262 | 384 |
| 1st quart. | 308 | 377 | 256 | 357 |
| 3rd quart. | 336 | 388 | 330 | 398 |
| <u>Ca Content (mg)</u> | | | | |
| Median | 119 | 138 | 95 | 140 |
| 1st quart. | 111 | 137 | 93 | 132 |
| 3rd quart. | 120 | 140 | 119 | 145 |
| <u>Dry Weight/Volume (mg/ml)</u> | | | | |
| Median | 716 | 770 | 593 | 768 |
| 1st quart. | 709 | 756 | 533 | 743 |
| 3rd quart. | 736 | 785 | 618 | 779 |
| <u>Ash Weight/Volume (mg/ml)</u> | | | | |
| Median | 460 | 490 | 356 | 484 |
| 1st quart. | 450 | 480 | 319 | 467 |
| 3rd quart. | 474 | 506 | 384 | 487 |
| <u>Ca Content/Volume (mg/ml)</u> | | | | |
| Median | 167 | 177 | 134 | 177 |
| 1st quart. | 164 | 174 | 116 | 170 |
| 3rd quart. | 172 | 181 | 158 | 179 |

b) Effect of PTH(1-37) by intravenous bolus administration on rats

Duration of treatment: 10 working days, once per day

Dose: 80 µg/kg/day

Infusion rate: 10 µg/kg/hour

5 Group 4: intravenous bolus administration
n = 7 - 10

| | Control | Group 4 Bolus iv |
|--------------------------------------|---------|---------------------|
| <u>Relative X-Ray Density (mmAl)</u> | | |
| Median | 1.0 | 1.3 |
| 1st quart. | 0.9 | 1.2 |
| 3rd quart. | 1.0 | 1.3 |
| <u>Length (mm)</u> | | |
| Median | 35 | 35 |
| 1st quart. | 35 | 34 |
| 3rd quart. | 35 | 36 |
| <u>Volume (µl)</u> | | |
| Median | 562 | 635 |
| 1st quart. | 522 | 624 |
| 3rd quart. | 641 | 714 |
| <u>Dry Weight (mg)</u> | | |
| Median | 449 | 517 |
| 1st quart. | 426 | 487 |
| 3rd quart. | 466 | 548 |
| <u>Ash Weight (mg)</u> | | |
| Median | 299 | 348 |
| 1st quart. | 293 | 329 |
| 3rd quart. | 313 | 366 |
| <u>Ca Content (mg)</u> | | |
| Median | 102 | 119 |
| 1st quart. | 101 | 114 |
| 3rd quart. | 106 | 126 |

| | Control | Group 4 Bolus iv |
|----------------------------------|---------|---------------------|
| <u>Dry Weight/Volume (mg/ml)</u> | | |
| Median | 771 | 800 |
| 1st quart. | 726 | 754 |
| 3rd quart. | 817 | 829 |
| <u>Ash Weight/Volume (mg/ml)</u> | | |
| Median | 513 | 527 |
| 1st quart. | 483 | 507 |
| 3rd quart. | 561 | 549 |
| <u>Ca Content/Volume (mg/ml)</u> | | |
| Median | 175 | 182 |
| 1st quart. | 165 | 176 |
| 3rd quart. | 191 | 189 |

Example 2

5

Iontophoretic application of PTH

A pilot experiment on transdermic application by iontophoresis was conducted on two rabbits. The animals were trimmed in the flanks, and the skin was cleaned with ethanol.

10 A filter paper soaked with hPTH(1-34) solution was placed on the skin and fixated with a chlorinated silver electrode. Iontophoresis was carried out over a time period of 90 and 105 minutes, respectively, under the following conditions: current intensity: 5-7 mA, current density: 0.44-0.62 mA/cm², current pulses: 8 ms at 2 ms intervals. During the experiment, blood was taken from the ear artery at various times (see table below), and

15 the serum obtained was deep frozen. Using the Nichols RIA INS-PTH, the PTH concentration in the serum samples was measured.

Result: In both animals, a significant level of hPTH(1-34) could be detected after a period of 1 to 1.5 hours.

hPTH(1-34) [pg/ml]

5

| | Time [min] | | | | | | | |
|----------|------------|-----|-----|-----|-----|------|------|------|
| | 0 | 20 | 30 | 45 | 60 | 90 | 105 | 120 |
| Animal 1 | 36 | 112 | | | 123 | 1834 | | |
| Animal 2 | 52 | | 107 | 112 | 391 | 915 | 1420 | 1315 |

CLAIMS:

1. A pharmaceutical administration form, containing parathyroid hormone (PTH) or a
5 parathyroid hormone derivative as the active ingredient, with an active ingredient
release period of from two to six hours.
2. The administration form according to claim 1, comprising an infusion solution for
continuous infusion of from two to six hours and preferably, four hours.
- 10 3. The administration form according to claim 1, comprising a transdermic pharmaceu-
tical system, preferably a patch or an iontophoretic system.
4. The administration form according to claim 1, comprising an enteric pharmaceutical
15 system, preferably loaded liposomes, or microspheres made of common polymers, or
proteinoid complexes.
5. The administration form according to one of claims 1 to 4, containing human
PTH(1-84).
- 20 6. The administration form according to one of claims 1 to 4, containing the N-terminal
fragments of human PTH comprising the sequences 1-29 through 1-41, preferably
1-34, 1-35, 1-36, 1-37, and 1-38.
- 25 7. Use of parathyroid hormone or parathyroid hormone derivatives for the preparation
of an administration form having an active ingredient release period of from two to
six hours.
8. The use according to claim 7 for the preparation of an infusion solution for
30 continuous infusion of from two to six hours and preferably, four hours.

9. The use according to claim 7 for the preparation of a transdermic or enteric administration form.
10. A method for osteoporosis treatment of the human body wherein, in order to increase the bone matter, a therapeutically effective amount of parathyroid hormone or parathyroid hormone derivative is applied in the form of a continuous infusion for two to six hours or a transdermic or enteric administration form having an active ingredient release period of from two to six hours.
11. The method according to claim 10, conducted within the scope of clinical tests for the purpose of authorization according to the drug law.
12. The method according to claim 10 or 11, wherein from 30 to 50 $\mu\text{g/kg/day}$ parathyroid hormone or parathyroid hormone derivative is used as therapeutically effective amount.
13. The method according to one of claims 10 to 12, wherein said continuous infusion is effected on 5 working days within two successive weeks.
14. The method according to one of claims 10 to 12, wherein said transdermic application is effected using a patch optionally containing permeation accelerators, or by iontophoresis.
15. The method according to one of claims 10 to 12, wherein said enteric application is effected using loaded liposomes, microspheres made of common polymers, or proteinoid complexes.

INTERNATIONAL SEARCH REPORT

International Application No

PC1/EP 96/01962

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/29 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | EP,A,0 643 981 (TAKEDA CHEMICAL INDUSTRIES) 22 March 1995 see claims 1,16,24,25 see page 6, line 47 - line 55 --- | 1,3,5-7, 9-12,14 |
| X | WO,A,87 00750 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 12 February 1987 see claims 10-12 see page 6, line 33 - page 7, line 18 see page 9, line 1 - line 10; table 2 --- | 1,4-7, 9-12,15 |
| A | WO,A,91 06564 (FORSSMAN, WOLF-GEORG) 16 May 1991 see claims 1,5,15 ----- | 1,2,7,8, 10-13 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/ 01962

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10-15 are directed to a method of treatment
of the human body, the search has been carried out and based on
the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
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of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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